

Table e-1. Frequencies of measurement by age

Age (y)	Classic Rett				Atypical Rett			
	Height	Weight	BMI	FOC	Height	Weight	BMI	FOC
0-1	1546	1872	1528	1365	163	190	162	133
1-2	668	946	663	628	62	93	62	57
2-3	538	791	533	487	41	56	41	36
3-4	463	665	460	413	46	59	46	39
4-5	458	594	456	394	48	50	48	43
5-6	377	470	375	341	40	45	40	34
6-7	321	402	316	272	27	32	26	23
7-8	258	373	256	207	22	26	22	14
8-9	250	342	250	205	35	40	33	29
9-10	205	273	202	175	34	36	33	28
10-11	205	261	204	170	31	32	31	25
11-12	138	176	137	129	25	26	25	21
12-13	113	152	113	100	20	25	20	16
13-14	82	129	82	72	15	17	15	12
14-15	82	123	82	79	15	16	15	14
15-16	62	87	61	62	9	11	9	8
16-17	52	73	52	51	6	6	6	6
17-18	52	65	52	43	8	8	8	8
18-19	52	70	51	45	2	2	2	1

19-20	43	56	43	40	2	2	2	2
>20	349	518	348	325	27	30	27	26
Total	6314	8438	6264	5603	678	802	673	575

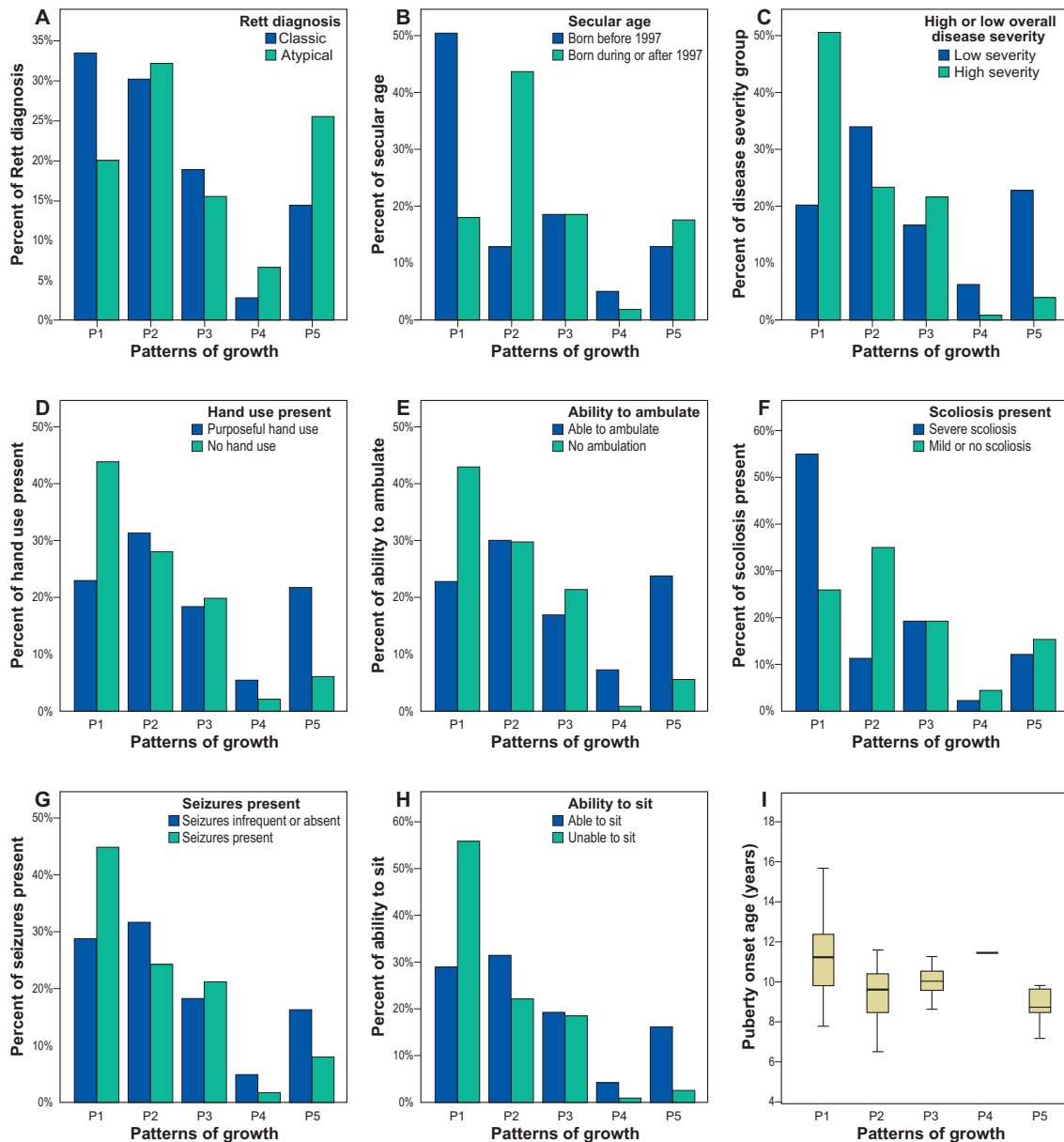
Table e-2. Association between growth parameters and functional severity
(standardized coefficients)

Rett Characteristic	Weight	Height	FOC	BMI
Overall severity score	-.27**	-.36**	-.16**	ns
Restricted hand use	-.12*	ns	-.27**	ns
Restricted ambulation	ns	-.29**	-.27**	ns
Poor nonverbal communication	ns	-.15*	-.10*	ns
Scoliosis severity	ns	-.28**	ns	ns
Seizure severity	ns	-.11*	-.12*	ns
Stereotypic frequency	-.08*	-.12*	ns	-.11*
Hyperventilation	-.13**	ns	-.13*	-.12*
Restricted independent sitting	ns	-.25**	-.18**	ns
Younger onset of regression	ns	ns	-.24**	-.09*

Abbreviations: FOC = fronto-occipital head circumference. BMI = body mass index. ** = significant at the $p < .001$ level. * = significant at the $p < .05$ level. ns = no significant association.

Note: the association is expressed as Beta, the strength of association represented by the slope of the line which that variable contributes to the regression equation. Specific relationships between growth and individual mutations are described in detail in the text body.

Figure e-1A-I. Patterns of growth among different Rett categories and attributes



Legend: Five patterns of growth among eight binary categories (Rett diagnosis, secular birth range, overall severity, five specific attributes of Rett disorder), and age of pubertal onset. Percent of each category with growth pattern indicated on y-axis for all but puberty onset (y=age in years). Growth patterns include: P1) severe weight and height deficit with microcephaly; P2) preserved, normal weight and height with microcephaly; P3) moderate

weight or height deficit with microcephaly; P4) weight and height deficit with preserved, normal head size; and P5) normal growth in all parameters. The boxplot in e1-I represents the middle 50% of the data, the dividing line is the median, and the whisker marks the most extreme data which are within 1.5 times the length of the box.

Appendix e-1. Growth Measurement Techniques

Basic Guidelines for Length Measurements Including Head Circumference and Height

- Always use flexible, non-stretchable tape measure
- Read all measurements at eye level and in good lighting
- Optimally it is best to use two people to position and hold participant and tape measure in correct position and record readings for each measure.
- Parents may also have to help hold, distract or calm the participant
- If exceptions are noted during exam (i.e. presence contractions, a cast, severe scoliosis, etc), try to follow guidelines but note exceptions when recording results.

Weight

Weight will be obtained at each visit in either a standing or sitting position and will be reported in kilograms (kg) to the nearest 0.1 kg.

Equipment: A beam scale with non-detachable weights or an equally accurate electronic scale can be used for participants who can stand. A chair or wheelchair (platform) scale may be used for participants who cannot stand. Prior to measuring, the scale should be calibrated. A standard weight should be used to check scale performance. If a platform or chair scale is not available or if the participant moves excessively, and if the participant is small enough to be held, the participant can be weighed while held in the arms of an adult.

The weight of the adult alone would be subtracted from the total weight, thus providing the weight of the participant.

Technique: Regardless of type of scale used, scale should be adjusted to zero. If a pad or sheet is used, zero the scale with these in place. If the participant is in a wheelchair, a tare weight of the chair is obtained after all extra bags and attachments have been removed and subtracted accordingly from the total weight of the participant and the wheelchair.

The chair tare weight can be recorded and used at the next visit if the wheelchair equipment does not change. Regardless of the type of scale, the participant should remove shoes, excess clothing and wet diaper and the weight is read either from the beam or the electronic readout. If there is excessive movement or if two separate measurements do not agree within 5 grams, take a third measurement and record an average of the three. Record the numerical value on data forms and plot on age-appropriate standardized form for weight.

Height

Height will be obtained at each visit and will be reported in centimeters (cm) to the nearest 0.1 cm. Participants who are able to stand should be measured in a standing position. Young participants or ones who are unable to stand will be measured in recumbent position. Participants with conditions such as scoliosis, kyphosis or contractures of legs or feet that prevent measurement by conventional recumbent methods will be measured with modified methods. Position of measurement (either standing, recumbent or calculated) should be noted on the data collection form

Standing Height Equipment: A vertical measuring rod, which is at least 175 cm high and capable of measuring to an accuracy of 0.1 cm should be used. A digital readout device is optimal.

Standing Height Technique: After removing the shoes, the participant should stand on a flat surface by the scale with feet parallel and with heels, buttocks, shoulders and back of head touching the upright. The head should be comfortably erect. The arms should be hanging loosely at the sides. The headpiece of the measuring device is gently lowered, crushing the hair and making contact with the top of the head. One observer should position the feet and straighten the knees, while a second observer positions the shoulders and holds the head erect, if necessary. Height is measured at the crown of the head, excluding hair accessories, pony tails or braids. Repeat the measurement until two measurements agree within 0.5 cm, average these and record the numerical value on data collection forms and plot on standardized form for height.

Recumbent Height Equipment: A firm, flat surface or a recumbent board, and a soft, non-stretchable measuring tape will be used.

Recumbent Height Technique: Two people are required to measure length accurately. The participant should be in recumbent position. Person “A” should hold the head with crown against the headboard or a flat surface so that the child is looking straight upward. Make sure the trunk and pelvis are properly aligned. Person “B” should straighten the child's legs and hold the ankles together with the toes pointed directly upward. With a flat surface pressed against the soles of the feet, mark the bottom of the foot and measure from the head to the mark at the foot. Repeat the procedure and measurement until two measurements agree within 0.2 cm (1/4 in).

Technique for calculation of height in the case of severe scoliosis or contractures: When an accurate height or length is not obtainable because of severe scoliosis or contractures, a conversion formula that considers regression between height (HT) and lower leg length (LLL) is used to calculate length. The LLL is equal to - 6.39 plus 0.354 times HT.

FOC

Head circumference will be obtained while the participant is in a seated position and will be reported in centimeters (cm) to the nearest 0.1 cm.

Equipment: A flexible, non-stretchable measuring tape will be used.

Technique: Objects such as pins or rubber bands will be removed from the hair. The measurer will stand to the side of the participant and will position the tape just superior to the eyebrows anteriorly and over the external occipital protuberance (inion) posteriorly. The tape should be pulled tightly to compress hair and braids should be removed or avoided. Measurements should be performed twice or until two measurements agree to within 0.1cm.

Leg length measurement

Leg length measurement of the lower leg length will be obtained at each visit and will be reported in centimeters to the nearest 0.1 cm.

Equipment: A flexible, non-stretchable measuring tape and a washable marker will be used. If available, a Ross™ knee height caliper can be used for the lower leg measurement.

Technique: Lower Leg length - If Ross™ calipers are not available, place participant in recumbent position on the exam table and locate the top of the patella. Place a removable mark on the table at the point adjacent to the patella. Flex foot to a 90 degree angle. Place

a removable mark on the table adjacent to the bottom of the heel. Measure the distance between marks for each leg and record. If Ross™ calipers are available, place the participant in the recumbent position on the exam table. Bend both the knee and the ankle to a 90 degree angle. Open the caliper and place the fixed blade under the heel. Press the sliding blade down against the thigh about 2 inches behind the patella. The shaft of the caliper should be in line with the tibia in the lower leg and over the lateral malleolus. To hold the measurement, push the locking lever away from the blades. Read the measurement through the viewing window. Release the locking lever by pushing it towards the caliper blades. Repeat the process twice until measurements within 0.5 cm are obtained. Repeat the technique for the other leg.

Body Mass Index

Body Mass Index will be calculated at each visit and reported in kg/m^2 .

Appendix e-2. Rett Syndrome Severity Scores

MOTOR-BEHAVIORAL ASSESSMENT

I. Behavioral/Social Assessment

1) Regression of motor skills	0	None
	1	Dyspraxia of gait/hand use
	2	Some gait and hand use
	3	Some gait or hand use
	4	No motor skills
2) Regression of verbal skills	0	Effective communication
	1	Consistently makes choices 50% of time
	2	Sometimes makes choices 10 - <50% of time
	3	Rarely makes choices 10% of time
	4	No communication
3) Poor eye/social contact	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time
4) Lack of sustained interest	0	None
	1	25% of time
	2	50% of time

		3	75% of time
		4	100% of time
5) Irritability, crying tantrums		0	None
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
6) Overactive/over passive	0	None	
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
7) Does not reach for objects or people	0	None	
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
8) Does not follow verbal commands, acts as deaf		0	None
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time

9) Feeding difficulties		0	None
		1	Occasional choking/gagging
		2	>30 minutes to feed
		3	Oral and gastrostomy feeding
		4	Gastrostomy only
10) Chewing difficulties	0		None
		1	Coarse chopped
		2	Fine chopped
		3	Pureed
		4	Gastrostomy
11) Lack of toilet training	0		Trained
		1	Continent during day
		2	Time trained, both urine and stool
		3	Time trained, stool
		4	Totally incontinent
12) Masturbation	0		None
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
13) Self-mutilation/pulling hair or ears, scratching, etc.	0		None
		1	25% of time
		2	50% of time

		3	75% of time
		4	100% of time
14) Aggressive behavior (head banging, throwing, spitting, etc.)	0	None	
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
15) Seizures	0	None	
		1	None, with medications
		2	Monthly, with or without medications
		3	Weekly, with or without medications
		4	Daily, with or without medications
16) Apparent insensitivity to pain	0	None	
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
Subtotal I		—	

II. Orofacial/Respiratory Assessment

17) Speech disturbance	0	Fluent	
		1	Phrases/sentences
		2	Words, <10
		3	Vocalizations, no words

	4	No utterances
18) Bruxism	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time
19) Breath holding	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time
20) Hyperventilation	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time
21) Air-saliva expulsion/drooling	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time
22) Mouthing of hands & objects	0	None
	1	25% of time

	2	50% of time
	3	75% of time
	4	100% of time

23) Biting self & others	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time

Subtotal II

—

III. Motor Assessment/Physical Signs

24) Hand clumsiness	0	Purposeful hand use
	1	Manipulates toys/switches
	2	Uses utensils/cup, may be adaptive
	3	Finger feeds only
	4	No purposeful hand use

25) Stereotypic hand washing, rubbing, clapping, stroking, kneading	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time

26) Ataxia/apraxia (gait & trunk)	0	None
	1	25% of time
	2	50% of time

		3	75% of time
		4	100% of time
27) Truncal rocking/shifting wt	0	None	
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
28) Oculogyric movements	0	None	
		1	25% of time
		2	50% of time
		3	75% of time
		4	100% of time
29) Bradykinesia	0	None	
		1	Occasional paucity of limb movement,
<10% of time			
		2	Some limb movement, <50% of time
		3	Occasional limb movement, <10% of time
		4	Severe lack of limb movement, 95-100% of
time			
30) Dystonia	0	None	
		1	Focal dystonia, ankle or wrist
		2	Focal dystonia, >1 extremity
		3	Generalized dystonia, >2 extremities
		4	Fixed positional deformity

31) Hypomimia	0	None
	1	Occasional facial immobility, <10% of time
	2	Some facial movement, <50% of time
	3	Occasional smiling, <10% of time
	4	No facial expression
32) Scoliosis	0	None
	1	1 - <20 degrees
	2	20 - <40 degrees
	3	≥40 degrees
	4	Surgery
33) Myoclonus	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time
34) Chorea/athetosis	0	None
	1	25% of time
	2	50% of time
	3	75% of time
	4	100% of time
35) Hypertonia/rigidity	0	None
	1	Ankle hypertonia/rigidity

		2	Upper or lower limb hypertonia/rigidity
		3	Generalized hypertonia without contractures
		4	Generalized hypertonia with contractures
36) Hyperreflexia	0		Normal muscle stretch reflexes
		1	4+ ankles or knees
		2	4+ ankles and knees
		3	4+ all extremities
		4	4+ all extremities with spread/clonus
37) Vasomotor disturbance	0		Warm, pink
		1	Cool, pink
		2	Cold, pink
		3	Cold, purple hands or feet
		4	Cold, purple hands and feet
	Subtotal III	—	
	Grand Total	—	

CLINICAL SEVERITY SCORE

I. Onset

1) Age of onset of regression	1	>30 mos
	2	18 mos to 30 mos
	3	12 mos to <18mos
	4	6 mos to <12 mos
	5	<6mos

II. Growth

2) Somatic growth at this visit	0	No growth failure (26 - 50th%)
	1	Decrease in BMI (11th - 25th%)
	2	Decrease in BMI (5th - 10th%)
	3	Decrease in BMI (<5th%)
	4	Decrease in BMI (<<5th%)
3) Head growth	0	None to minimal deceleration (0-1 centile)
	1	Deceleration >2 centiles, OFC >10th after
24 mos		
	2	2nd - 10th centile after 24 mos
	3	2nd - 10th centile before 24 mos
	4	<2nd centile by 24 mos

III. Motor

4) Independent sitting at this visit by exam	0	Sits alone acquired ≤ 8 mos
	1	Sit with delayed acquisition >8 mos
	2	Sit with delayed acquisition >18 mos
	3	Sit with delayed acquisition >30 mos
	4	Lost
	5	Never acquired
5) Ambulation at this visit by exam	0	Acquired <18 mos/Apraxic gait
	1	18 mos \leq walks alone \leq 30mos
	2	>30 mos walks alone
	3	>50 mos walks with help
	4	Lost

	5	Never acquired
6) Hand use	0	Acquired & conserved
8 mos)	1	Holding of objects acquired on time (by 6 -
		& partially conserved
	2	Holding of objects acquired late (>10 mos)
		& partially conserved
acquisitions	3	Holding of objects acquired & lost all
nose)		(except for example scratching, rubbing
	4	Never acquired
7) Scoliosis	0	None
	1	1 - <20 degrees
	2	20 - <40 degrees
	3	40 - <60 degrees
	4	≥60 degrees
	5	Surgery

IV. Communication

8) Language at this visit by exam	0	Preserved, contextual
	1	Short phrases only
	2	Single words
	3	Vocalization, babbling
	4	Screaming, no utterances

9) Nonverbal Communication at this visit	0	Preserved and propositive
by exam		(points consistently with finger or eyes)
	1	Good eye contact maintained (≥ 30 seconds)
	2	Intermittent eye contact (5 seconds to < 30 seconds)
	3	Infrequent eye contact (< 5 seconds)
	4	Lost and not regained
	5	None

V. Rett Behaviors/Other neurologic

10) Respiratory dysfunction at this visit	0	None
by exam	1	Minimal hyperventilation and/or apnea ($< 10\%$ of time)
	2	Intermittent hyperventilation and/or apnea (50% of time)
	3	Constant hyperventilation and/or apnea without cyanosis (100% of time)
	4	Constant hyperventilation and/or apnea with cyanosis
11) Autonomic symptoms at this visit	0	None
by exam	1	Pink but cool
	2	Mottled and cold
	3	Blue-purple and cold hands or feet
	4	Blue-purple and cold hands and feet
12) Onset of stereotypes	0	≥ 10 years
	1	36 mos to < 10 years

		2	18 to <36 mos
		3	12 to <18 mos
		4	<12 mos
13) Epilepsy/Seizures at this visit	0	Absent	
		1	<Monthly
		2	<Weekly to monthly
		3	Weekly
		4	More than weekly
		5	Infantile spasms
TOTAL SCORE	—		